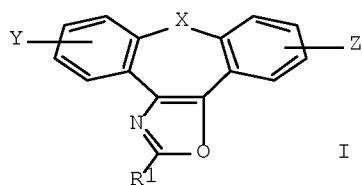


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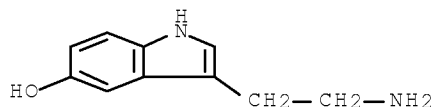
L7 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2005:471961 HCAPLUS Full-text
 DOCUMENT NUMBER: 143:1314
 TITLE: Use of 3-aza-1-oxa-dibenzo[e,h]azulenes for the
 manufacture of pharmaceutical formulations for the
 treatment and prevention of central nervous system
 diseases and disorders
 INVENTOR(S): Mercep, Mladen; Mesic, Milan;
 Pesic, Dijana; Dzapov, Iva
 PATENT ASSIGNEE(S): Pliva-Istrazivacki Institut D.O.O., Croatia
 SOURCE: PCT Int. Appl., 38 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005049036	A1	20050602	WO 2004-HR54	20041119
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2546591	A1	20050602	CA 2004-2546591	20041119
EP 1684766	A1	20060802	EP 2004-798733	20041119
EP 1684766	B1	20070627		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR, IS, YU				
CN 1901918	A	20070124	CN 2004-80039454	20041119
JP 2007512308	T	20070517	JP 2006-540631	20041119
AT 365556	T	20070715	AT 2004-798733	20041119
ES 2289573	T3	20080201	ES 2004-798733	20041119
IN 2006CN02229	A	20070608	IN 2006-CN2229	20060621
US 20070111990	A1	20070517	US 2006-595938	20060811
HK 1098670	A1	20080104	HK 2007-101111	20070131
PRIORITY APPLN. INFO.:			HR 2003-959	A 20031121
			WO 2004-HR54	W 20041119
OTHER SOURCE(S):	MARPAT 143:1314			
GI				



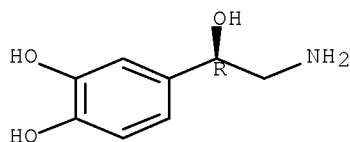
- AB The present invention relates to the use of compds. from the group of 3-aza-1-oxadibenzo[e,h]azulenes (I; X = heteroatom such as O, S, SO, SO₂, (un)protected NH; Y, Z = H, halo, alkyl, alkenyl, hydroxy, amino, thiol, sulfonyl, cyano, nitro, etc.; R₁ = H, CHO, alkyl, carboxylic, etc.) and of their pharmacol. acceptable salts and solvates for the manufacture of a pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system (CNS) caused by disorders of the neurochem. equilibrium of biogenic amines or other neurotransmitters. Thus, an in vitro affinity of I compds. for binding to recombinant human 5-HT_{2A} and 5-HT_{2C} serotonin receptors expressed in CHO-K1 or COS-7 cells was determined using a radioligand. The radioligand binding was inhibited by the test compds. proportionally to the affinity of a certain compound for the receptor and to the concentration of the compound. Compds. showing IC₅₀ and K_i in concns. lower than 1 μM were considered to be active. Compds. 1-oxa-8-thia-3-azadibenzo[e,h]azulene, dimethyl[2-(1-oxa-8-thia-3-azadibenzo[e,h]azulen-2-ylmethoxy)ethyl]amine, [2-(1-chloro-1-oxa-8-thia-3-azadibenzo[e,h]azulen-2-ylmethoxy)ethyl]dimethylamine, [2-(5-chloro-1-oxa-8-thia-3-azadibenzo[e,h]azulen-2-ylmethoxy)ethyl]dimethylamine and 5-chloro-2-methyl-1,8-dioxa-3-azadibenzo[e,h]azulene showed binding affinity to 5-HT_{2A} and 5-HT_{2C} receptors expressed as IC₅₀ value less than 200 nM and K_i value less than 100 nM.
- IC ICM A61K031-55
ICS A61K031-424; A61P025-00; A61P025-18; A61P025-22; A61P025-24
- CC 1-11 (Pharmacology)
Section cross-reference(s): 63
- ST azaoxadibenzoazulene biogenic amine neurotransmitter nervous system disease; dibenzoazulene azaoxa biogenic amine neurotransmitter CNS disease
- IT Central nervous system, disease
Human
(azaoxa-dibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT Neurotransmitters
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(azaoxa-dibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT Amines, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(biogenic; azaoxa-dibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT 5-HT receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type 5-HT_{2A}, binding to; azaoxa-dibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT 5-HT receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type 5-HT_{2C}, binding to; azaoxa-dibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)

- IT Opioid receptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (δ 1-opioid, binding to; azaoxa-dibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT 50-67-9, Serotonin, biological studies 51-41-2,
 Norepinephrine 51-61-6, Dopamine, biological studies
 56-86-0, L-Glutamic acid, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (azaoxa-dibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT 612837-28-2, Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole
 612837-29-3, Dibenzo[2,3:6,7]oxepino[4,5-d]oxazole
 612837-30-6 612837-31-7 612837-32-8
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 612837-56-6 612837-57-7 612837-58-8
 612837-59-9 612837-60-2 612837-61-3
 612837-62-4 612837-63-5 612837-64-6
 612837-65-7 612837-66-8 612837-67-9
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (azaoxa-dibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT 50-67-9, Serotonin, biological studies 51-41-2,
 Norepinephrine 51-61-6, Dopamine, biological studies
 56-86-0, L-Glutamic acid, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (azaoxa-dibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- RN 50-67-9 HCAPLUS
- CN 1H-Indol-5-ol, 3-(2-aminoethyl)- (CA INDEX NAME)



- RN 51-41-2 HCAPLUS
- CN 1,2-Benzenediol, 4-[(1R)-2-amino-1-hydroxyethyl]- (CA INDEX NAME)

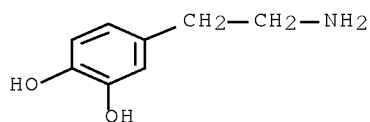
Absolute stereochemistry. Rotation (-).



- RN 51-61-6 HCAPLUS

10/595,935

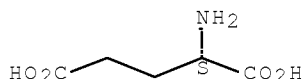
CN 1,2-Benzenediol, 4-(2-aminoethyl)- (CA INDEX NAME)



RN 56-86-0 HCAPLUS

CN L-Glutamic acid (CA INDEX NAME)

Absolute stereochemistry.



IT 612837-28-2, Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole

612837-29-3, Dibenz[2,3:6,7]oxepino[4,5-d]oxazole

612837-30-6 612837-31-7 612837-32-8

612837-33-9 612837-34-0 612837-35-1

612837-36-2 612837-37-3 612837-38-4

612837-39-5 612837-40-8 612837-41-9

612837-42-0 612837-43-1 612837-44-2

612837-46-4 612837-47-5 612837-48-6

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612837-52-2 612837-53-3 612837-54-4

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612837-59-9 612837-60-2 612837-61-3

612837-62-4 612837-63-5 612837-64-6

612837-65-7 612837-66-8 612837-67-9

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(aza-oxa-dibenzoazulenes for treatment and prevention of CNS disorders
by modulating biogenic amines or other neurotransmitters)

RN 612837-28-2 HCAPLUS

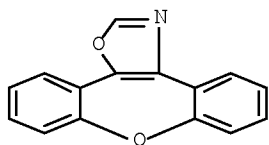
CN Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole (9CI) (CA INDEX NAME)



RN 612837-29-3 HCAPLUS

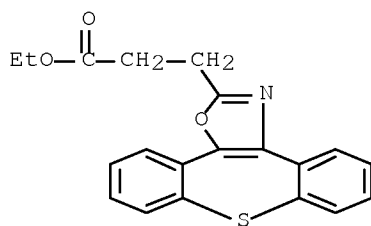
CN Dibenz[2,3:6,7]oxepino[4,5-d]oxazole (9CI) (CA INDEX NAME)

10/595,935



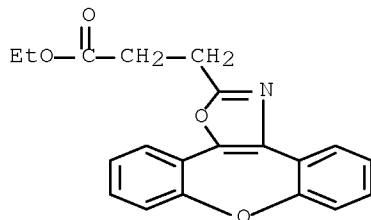
RN 612837-30-6 HCAPLUS

CN Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole-2-propanoic acid, ethyl ester (CA INDEX NAME)



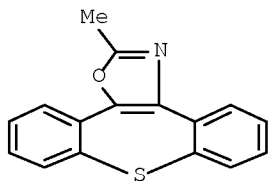
RN 612837-31-7 HCAPLUS

CN Dibenzo[2,3:6,7]oxepino[4,5-d]oxazole-2-propanoic acid, ethyl ester (CA INDEX NAME)



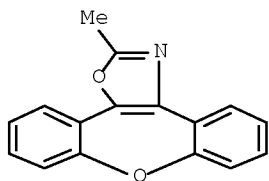
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CN Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole, 2-methyl- (CA INDEX NAME)

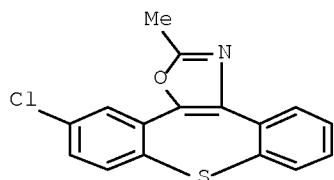


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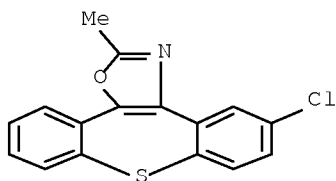
CN Dibenzo[2,3:6,7]oxepino[4,5-d]oxazole, 2-methyl- (CA INDEX NAME)



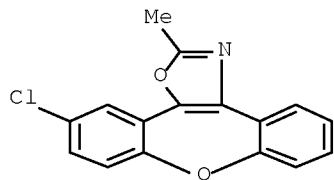
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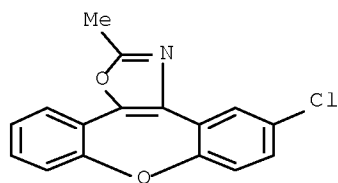
RN 612837-35-1 HCAPLUS
 CN Dibenzo[2,3:6,7]thienopyrazole, 5-chloro-2-methyl- (CA INDEX NAME)



RN 612837-36-2 HCAPLUS
 CN Dibenzo[2,3:6,7]thienopyrazole, 11-chloro-2-methyl- (CA INDEX NAME)

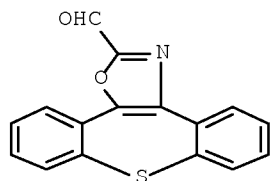


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 CN Dibenzo[2,3:6,7]thienopyrazole, 5-chloro-2-methyl- (CA INDEX NAME)



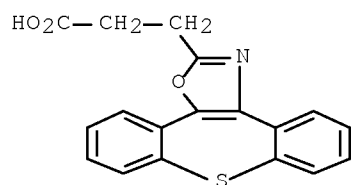
RN 612837-38-4 HCAPLUS

CN Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole-2-carboxaldehyde (CA INDEX NAME)



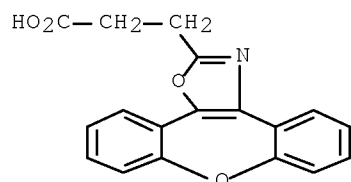
RN 612837-39-5 HCAPLUS

CN Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole-2-propanoic acid (CA INDEX NAME)



RN 612837-40-8 HCAPLUS

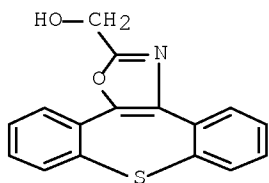
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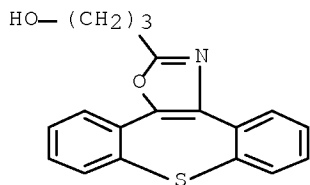
CN Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole-2-methanol (CA INDEX NAME)

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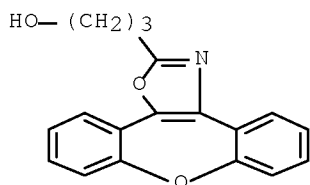
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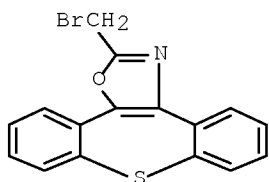
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CN Dibenzo[2,3:6,7]oxepino[4,5-d]oxazole-2-propanol (CA INDEX NAME)



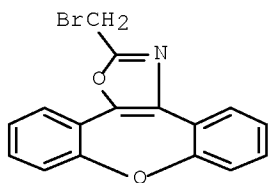
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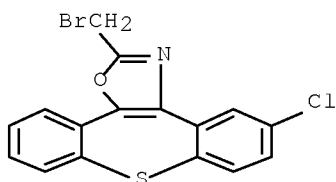


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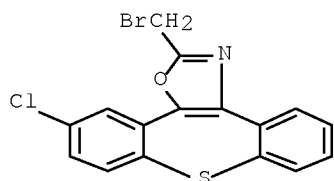
CN Dibenzo[2,3:6,7]oxepino[4,5-d]oxazole, 2-(bromomethyl)- (CA INDEX NAME)



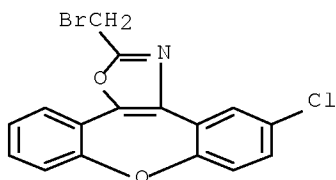
RN 612837-47-5 HCAPLUS
 CN Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole, 2-(bromomethyl)-5-chloro- (CA INDEX NAME)



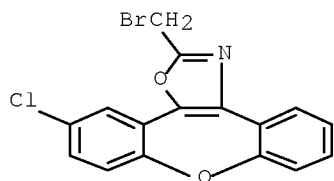
RN 612837-48-6 HCAPLUS
 CN Dibenzo[2,3:6,7]thiepino[4,5-d]oxazole, 2-(bromomethyl)-11-chloro- (CA INDEX NAME)



RN 612837-49-7 HCAPLUS
 CN Dibenz[2,3:6,7]oxepino[4,5-d]oxazole, 2-(bromomethyl)-5-chloro- (CA INDEX NAME)

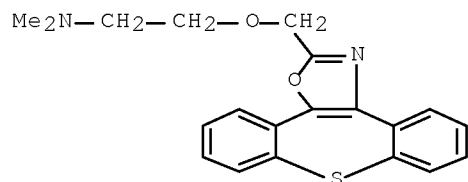


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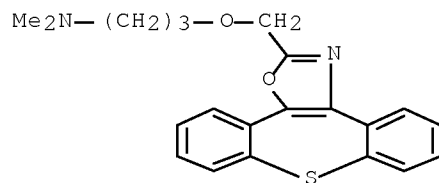
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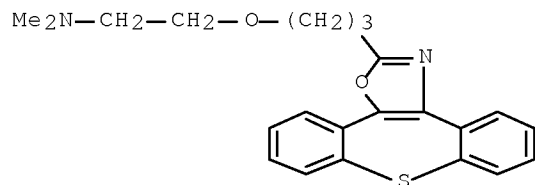
RN 612837-52-2 HCAPLUS

CN 1-Propanamine, 3-(dibenzo[2,3:6,7]thiepino[4,5-d]oxazol-2-ylmethoxy)-N,N-dimethyl- (CA INDEX NAME)



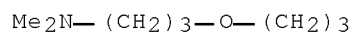
RN 612837-53-3 HCAPLUS

CN Ethanamine, 2-(3-dibenzo[2,3:6,7]thiepino[4,5-d]oxazol-2-ylpropoxy)-N,N-dimethyl- (CA INDEX NAME)



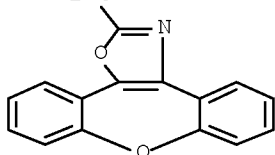
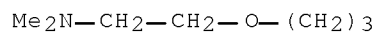
RN 612837-54-4 HCAPLUS

CN 1-Propanamine, 3-(3-dibenzo[2,3:6,7]thiepino[4,5-d]oxazol-2-ylpropoxy)-N,N-dimethyl- (CA INDEX NAME)



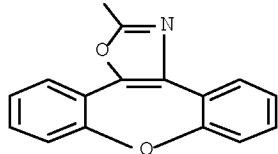
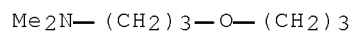
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CN Ethanamine, 2-(3-dibenz[2,3:6,7]oxepino[4,5-d]oxazol-2-ylpropoxy)-N,N-dimethyl- (CA INDEX NAME)



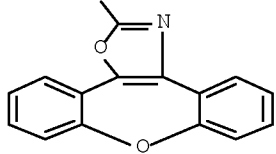
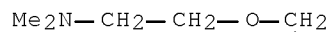
RN 612837-57-7 HCAPLUS

CN 1-Propanamine, 3-(3-dibenz[2,3:6,7]oxepino[4,5-d]oxazol-2-ylpropoxy)-N,N-dimethyl- (CA INDEX NAME)



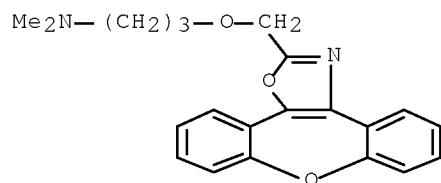
RN 612837-58-8 HCAPLUS

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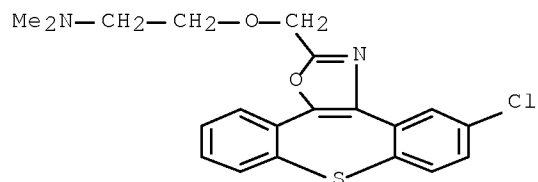
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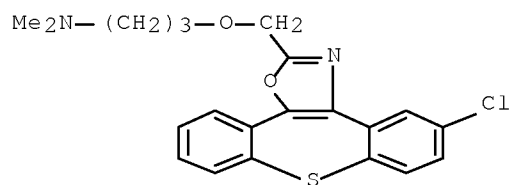
RN 612837-60-2 HCAPLUS

CN Ethanamine, 2-[(5-chlorodibenzo[2,3:6,7]thiepino[4,5-d]oxazol-2-yl)methoxy]-N,N-dimethyl- (CA INDEX NAME)



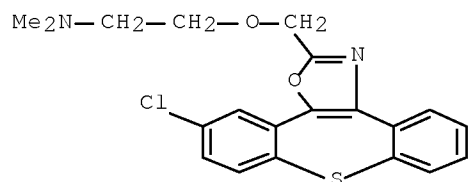
RN 612837-61-3 HCAPLUS

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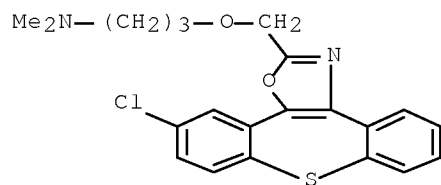
RN 612837-62-4 HCAPLUS

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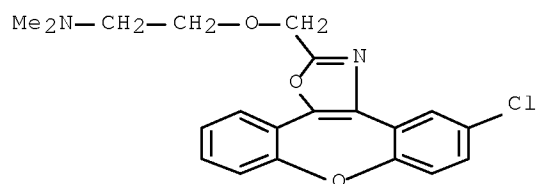
RN 612837-63-5 HCAPLUS

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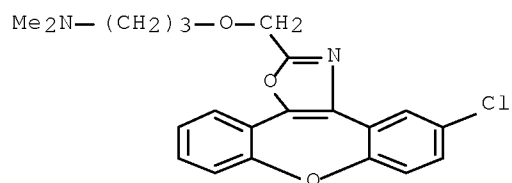
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CN Ethanamine, 2-[(5-chlorodibenz[2,3:6,7]oxepino[4,5-d]oxazol-2-yl)methoxy]-N,N-dimethyl- (CA INDEX NAME)



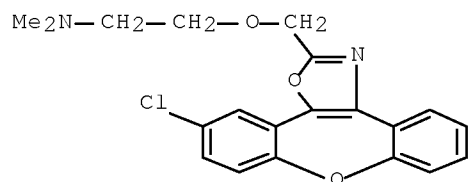
RN 612837-65-7 HCAPLUS

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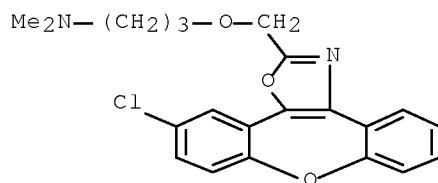
RN 612837-66-8 HCAPLUS

CN Ethanamine, 2-[(11-chlorodibenz[2,3:6,7]oxepino[4,5-d]oxazol-2-yl)methoxy]-N,N-dimethyl- (CA INDEX NAME)



RN 612837-67-9 HCAPLUS

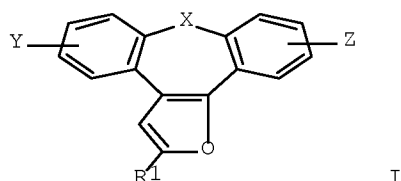
CN 1-Propanamine, 3-[(11-chlorodibenz[2,3:6,7]oxepino[4,5-d]oxazol-2-yl)methoxy]-N,N-dimethyl- (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN
 ACCESSION NUMBER: 2005:471937 HCAPLUS Full-text
 DOCUMENT NUMBER: 143:1311
 TITLE: Use of 1-oxadibenzo[e,h]azulenes
 for the manufacture of pharmaceutical formulations for
 the treatment and prevention of central nervous system
 diseases and disorders
 INVENTOR(S): Mercep, Mladen; Mesic, Milan;
 Pesic, Dijana
 PATENT ASSIGNEE(S): Pliva-Istrazivacki Institut D.O.O., Croatia
 SOURCE: PCT Int. Appl., 37 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
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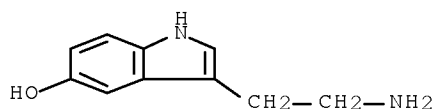
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WO 2005049010	A1	20050602	WO 2004-HR52	20041119
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PRIORITY APPLN. INFO.:			HR 2003-955	A 20031121
			WO 2004-HR52	W 20041119
OTHER SOURCE(S):		MARPAT 143:1311		
GI				



- AB The present invention relates to the use of compds. from the group of 1-oxadibenzo[e,h]azulenes (I; X = CH₂, heteroatom such as O, S, SO, SO₂, amino; Y, Z = H, halo, alkyl, haloalkyl, hydroxy, alkoxy, amino, thiol, sulfonyl, carboxy, cyano, nitro, etc.; R₁ = CHO, alkyl, amino, etc.) and of their pharmacol. acceptable salts and solvates for the manufacture of a pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system (CNS) caused by disorders of the neurochem. equilibrium of biogenic amines or other neurotransmitters, such as serotonin, norepinephrine and dopamine. Thus, an in vitro affinity of I compds. for binding to recombinant human 5-HT_{2A} and 5-HT_{2C} serotonin receptors expressed in CHO-K1 or COS-7 cells was determined using a radioligand. The radioligand binding was inhibited by the test compds. proportionally to the affinity of a certain compound for the receptor and to the concentration of the compound Compds. showing IC₅₀ and K_i in concns. lower than 1 μM were considered to be active. Compound 2-[(11-chloro-1,8-dioxadibenzo[e,h]azulen-2-yl- methoxy)ethyl]dimethylamine showed binding affinity to 5-HT_{2A} and 5-HT_{2C} receptors expressed as IC₅₀ value less than 200 nM and K_i value less than 100 nM.
- IC ICM A61K031-343
- ICS A61K031-34; A61K031-38; A61K031-55; A61P025-00
- CC 1-11 (Pharmacology)
- Section cross-reference(s): 63
- ST oxadibenzoazulene biogenic amine neurotransmitter central nervous system disease; dibenzoazulene oxa biogenic amine neurotransmitter CNS disease
- IT Amines, biological studies
- RL: BSU (Biological study, unclassified); BIOL (Biological study) (biogenic; oxadibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT Central nervous system, disease
- Human
- (oxadibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT Neurotransmitters
- RL: BSU (Biological study, unclassified); BIOL (Biological study) (oxadibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT 5-HT receptors
- RL: BSU (Biological study, unclassified); BIOL (Biological study) (type 5-HT_{2A}, binding to; oxadibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT 5-HT receptors
- RL: BSU (Biological study, unclassified); BIOL (Biological study) (type 5-HT_{2C}, binding to; oxadibenzoazulenes for treatment and prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)
- IT Opioid receptors
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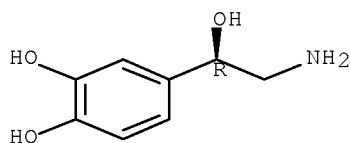
prevention of CNS disorders by modulating biogenic amines or other neurotransmitters)

- IT 50-67-9, Serotonin, biological studies 51-41-2,
Norepinephrine 51-61-6, Dopamine, biological studies
56-86-0, L-Glutamic acid, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(oxadibenzoazulenes for treatment and prevention of CNS disorders by
modulating biogenic amines or other neurotransmitters)
- IT 199012-94-7D, Dibenzo[b,f]furo[2,3-d]oxepin, derivs.
628262-96-4 628262-97-5 628262-98-6
628262-99-7 628263-00-3 628263-01-4
628263-02-5 628263-03-6 628263-04-7,
Dibenzo[b,f]furo[2,3-d]oxepin-2-methanol 628263-05-8
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oxadibenzoazulenes for treatment and prevention of CNS disorders by
modulating biogenic amines or other neurotransmitters)
- IT 50-67-9, Serotonin, biological studies 51-41-2,
Norepinephrine 51-61-6, Dopamine, biological studies
56-86-0, L-Glutamic acid, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(oxadibenzoazulenes for treatment and prevention of CNS disorders by
modulating biogenic amines or other neurotransmitters)
- RN 50-67-9 HCAPLUS
CN 1H-Indol-5-ol, 3-(2-aminoethyl)- (CA INDEX NAME)

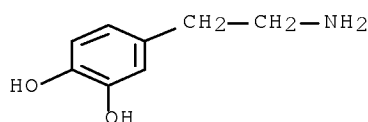


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Absolute stereochemistry. Rotation (-).

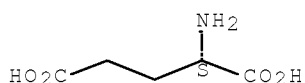


- RN 51-61-6 HCAPLUS
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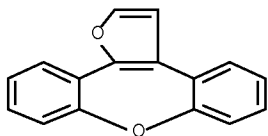


- RN 56-86-0 HCAPLUS
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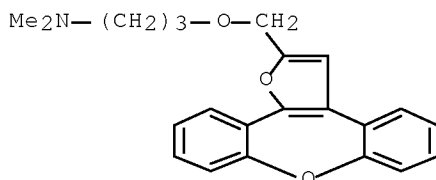
Absolute stereochemistry.



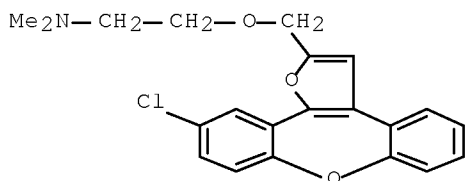
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 628263-02-5 628263-03-6 628263-04-7,
 Dibenzo[b,f]furo[2,3-d]oxepin-2-methanol 628263-05-8
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (oxadibenzoazulenes for treatment and prevention of CNS disorders by
 modulating biogenic amines or other neurotransmitters)
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 CN Dibenzo[b,f]furo[2,3-d]oxepin (9CI) (CA INDEX NAME)



RN 628262-96-4 HCAPLUS
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 (CA INDEX NAME)



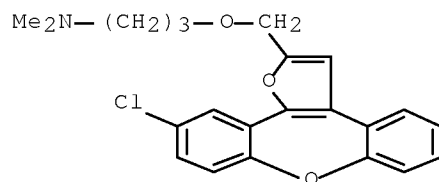
RN 628262-97-5 HCAPLUS
 CN Ethanamine, 2-[(11-chlorodibenzo[b,f]furo[2,3-d]oxepin-2-yl)methoxy]-N,N-
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RN 628262-98-6 HCAPLUS

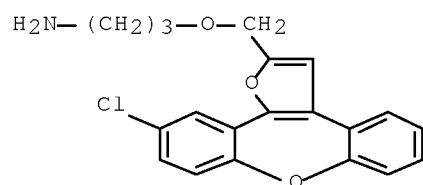
10/595,935

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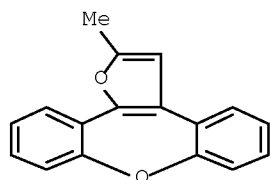
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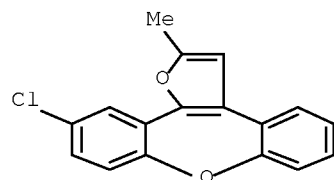
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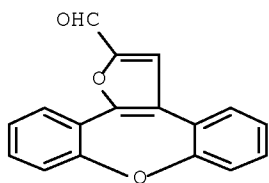
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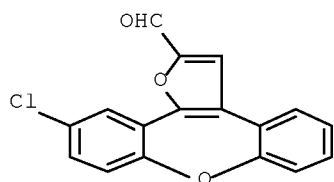
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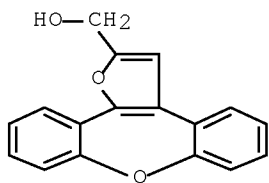
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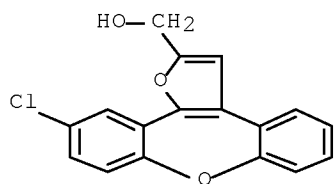
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CN Dibenzo[b,f]furo[3,2-d]oxepin-2-methanol (CA INDEX NAME)



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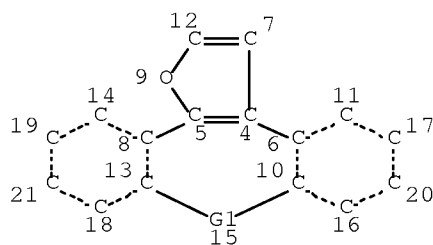
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THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

RESULTS FROM REGISTRY, CAPLUS, AND USPATFULL

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE

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L15 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:471937 HCAPLUS Full-text
DOCUMENT NUMBER: 143:1311
TITLE: Use of 1-oxadibenzo[e,h]azulenes for the manufacture
of pharmaceutical formulations for the treatment and
prevention of central nervous
system diseases and disorders
INVENTOR(S): Mercep, Mladen; Mesic, Milan; Pesic, Dijana
PATENT ASSIGNEE(S): Pliva-Istrazivacki Institut D.O.O., Croatia
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

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EP 1684742 A1 20060802 EP 2004-798731 20041119 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR, IS, YU

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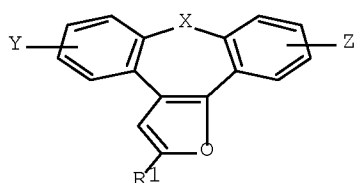
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PRIORITY APPLN. INFO.: HR 2003-955 A 20031121 <--

WO 2004-HR52 W 20041119

OTHER SOURCE(S): MARPAT 143:1311

GI



I

AB The present invention relates to the use of compds. from the group of 1-oxadibenzo[e,h]azulenes (I; X = CH₂, heteroatom such as O, S, SO, SO₂, amino; Y, Z = H, halo, alkyl, haloalkyl, hydroxy, alkoxy, amino, thiol, sulfonyl, carboxy, cyano, nitro, etc.; R₁ = CHO, alkyl, amino, etc.) and of their pharmacol. acceptable salts and solvates for the manufacture of a pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system (CNS) caused by disorders of the neurochem. equilibrium of biogenic amines or other neurotransmitters, such as serotonin, norepinephrine and dopamine. Thus, an in vitro affinity of I compds. for binding to recombinant human 5-HT_{2A} and 5-HT_{2C} serotonin receptors expressed in CHO-K1 or COS-7 cells was determined using a radioligand. The radioligand binding was inhibited by the test compds. proportionally to the affinity of a certain compound for the receptor and to the concentration of the compound Compds. showing IC₅₀ and K_i in concns. lower than 1 μM were considered to be active. Compound 2-[(11-chloro-1,8-dioxadibenzo[e,h]azulen-2-yl- methoxy)ethyl]dimethylamine showed binding affinity to 5-HT_{2A} and 5-HT_{2C} receptors expressed as IC₅₀ value less than 200 nM and K_i value less than 100 nM.

IT 199012-94-7D, Dibenzo[b,f]furo[2,3-d]oxepin, derivs.

628262-96-4 628262-97-5 628262-98-6

628262-99-7 628263-00-3 628263-01-4

628263-02-5 628263-03-6 628263-04-7,

Dibenzo[b,f]furo[2,3-d]oxepin-2-methanol 628263-05-8

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

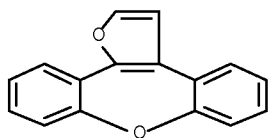
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disorders by modulating biogenic amines or other

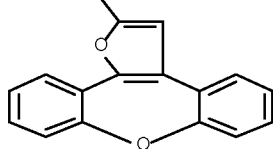
neurotransmitters)

RN 199012-94-7 HCAPLUS

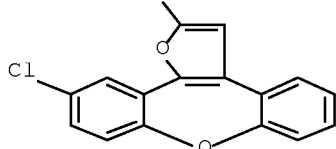
CN Dibenzo[b,f]furo[2,3-d]oxepin (9CI) (CA INDEX NAME)



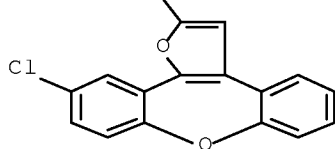
RN 628262-96-4 HCAPLUS

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RN 628262-97-5 HCAPLUS

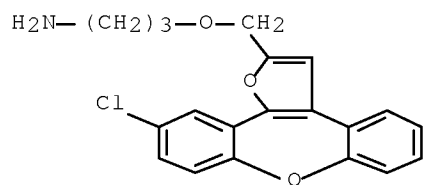
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(CA INDEX NAME)Me₂N—CH₂—CH₂—O—CH₂

RN 628262-98-6 HCAPLUS

CN 1-Propanamine, 3-[(11-chlorodibenzo[b,f]furo[2,3-d]oxepin-2-yl)methoxy]-N,N-dimethyl-
(CA INDEX NAME)Me₂N—(CH₂)₃—O—CH₂

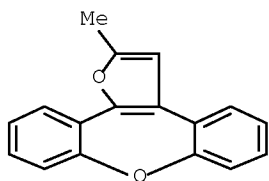
RN 628262-99-7 HCAPLUS

CN 1-Propanamine, 3-[(11-chlorodibenzo[b,f]furo[2,3-d]oxepin-2-yl)methoxy]-
(CA INDEX NAME)



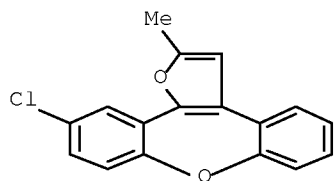
RN 628263-00-3 HCAPLUS

CN Dibenzo[b,f]furo[3,2-d]oxepin, 2-methyl- (CA INDEX NAME)



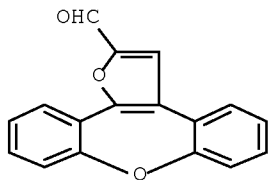
RN 628263-01-4 HCAPLUS

CN Dibenzo[b,f]furo[2,3-d]oxepin, 11-chloro-2-methyl- (CA INDEX NAME)



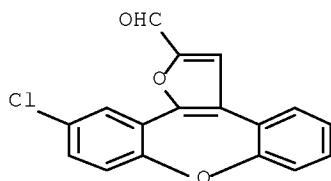
RN 628263-02-5 HCAPLUS

CN Dibenzo[b,f]furo[3,2-d]oxepin-2-carboxaldehyde (CA INDEX NAME)

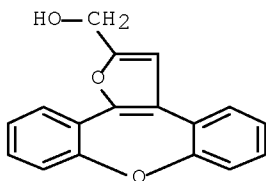


RN 628263-03-6 HCAPLUS

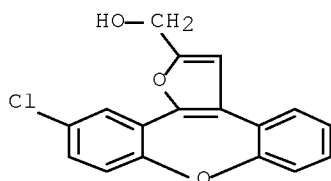
CN Dibenzo[b,f]furo[3,2-d]oxepin-2-carboxaldehyde, 11-chloro- (CA INDEX NAME)



RN 628263-04-7 HCAPLUS
 CN Dibenzo[b,f]furo[3,2-d]oxepin-2-methanol (CA INDEX NAME)



RN 628263-05-8 HCAPLUS
 CN Dibenzo[b,f]furo[3,2-d]oxepin-2-methanol, 11-chloro- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1983:143257 HCAPLUS [Full-text](#)

DOCUMENT NUMBER: 98:143257

ORIGINAL REFERENCE NO.: 98:21821a,21824a

TITLE: Neurotropic and psychotropic agents. CLXXIII.
 Fluorinated tricyclic neuroleptics with prolonged
 action: 3-fluoro-10-[4-(2-hydroxyethyl)piperazino]-
 10,11-dihydrodibenzo[b,f]thiepins with less common
 substituents in position 8

AUTHOR(S): Sindelar, Karel; Metysova, Jirina; Holubek, Jiri;
 Svatek, Emil; Ryska, Miroslav; Protiva, Miroslav

CORPORATE SOURCE: Res. Inst. Pharm. Biochem., Prague, 130 60, Czech.
 SOURCE: Collection of Czechoslovak Chemical Communications (1983), 48(1), 144-55

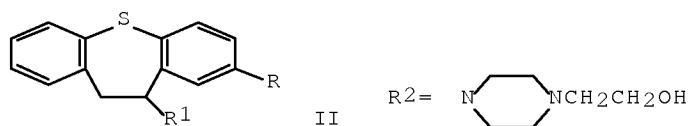
CODEN: CCCCAK; ISSN: 0366-547X

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 98:143257

GI

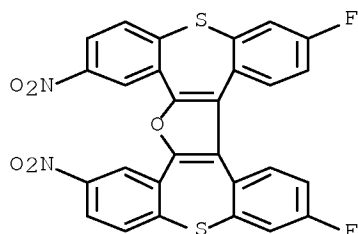


AB Cyclization of 4,2-F(4-O2NC6H4S)C6H3CO2H gave 3-fluoro-8-nitrodibenzo[b,f]thiepin-10(11H)-one (I). I was reduced to II (R = NO2, R1 = OH) which was chlorinated to II (R = NO2, R1 = Cl)(III). Condensation of III with R2H gave II (R = NO2, R1 = R2). Also prepared were II (R = NH2, Ac, SO2NMe; R1 = R2). These II are central nervous system depressants and apomorphine antagonists. I (R = NO2, R1 = R2) had ED50 of 0.27 mg/kg orally in mice in the rotarod test after 2 h compared to 2.2 mg/kg for octoclotheptsin.

IT 85195-81-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 85195-81-9 HCAPLUS

CN Bisdibenzo[2,3:6,7]thiepin[4,5-b:4',5'-d]furan, 12,17-difluoro-3,7-dinitro- (9CI) (CA INDEX NAME)



L15 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1982:85513 HCAPLUS [Full-text](#)

DOCUMENT NUMBER: 96:85513

ORIGINAL REFERENCE NO.: 96:14043a

TITLE: Neurotropic and psychotropic agents. CLIV.
Fluorinated tricyclic neuroleptics with prolonged
action: 3-fluoro-8-halo derivatives of
10-piperazino-10,11-dihydrodibenzo[b,f]thiepins

AUTHOR(S): Protiva, Miroslav; Sindelar, Karel; Metysova, Jirina;
Holubek, Jiri; Ryska, Miroslav; Svatek, Emil; Sedivy,
Zdenek; Pomykacek, Josef

CORPORATE SOURCE: Res. Inst. Pharm. Biochem., Prague, 130 60, Czech.

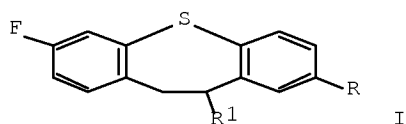
SOURCE: Collection of Czechoslovak Chemical Communications (1981), 46(8), 1788-99
CODEN: CCCCAK; ISSN: 0366-547X

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 96:85513

GI



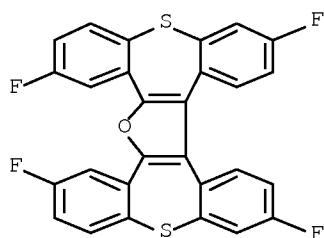
AB The title compds. I [R = F, R1 = 4-methylpiperazino; R = Br, iodo, R1 = 4-(2-hydroxyethyl)piperazino] were prepared by aminating I (R1 = Cl), obtained by chlorinating I (R1 = OH). The alcs. were obtained by reducing the ketones, prepared by cyclizing 5,2-F(HO2CCH2)C6H3SC6H4R-4 with polyphosphoric acid. I (R1 = substituted piperazino) have central nervous system depressant activity. Their structure-activity relationships are discussed.

IT 80709-39-3P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 80709-39-3 HCAPLUS

CN Bisdibenzo[2,3:6,7]thiepine[4,5-b:4',5'-d]furan, 3,7,12,17-tetrafluoro-
(9CI) (CA INDEX NAME)



L15 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1980:146715 HCAPLUS Full-text

DOCUMENT NUMBER: 92:146715

ORIGINAL REFERENCE NO.: 92:23848h,23849a

TITLE: Neurotropic and psychotropic agents. CXXVII.
Potential metabolites of tricyclic neuroleptics and
their fluorinated analogs; 3-hydroxy-, 3-methoxy- and
3-fluoro-10-(4-methylpiperazino)-10,11-
dihydrodibenzo[b,f]thiepin

AUTHOR(S): Protiva, Miroslav; Sindelar, Karel; Sedivy, Zdenek;
Metysova, Jirina

CORPORATE SOURCE: Res. Inst. Pharm. Biochem., Prague, 130 00/3, Czech.

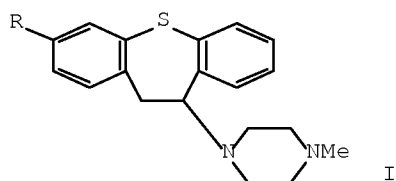
SOURCE: Collection of Czechoslovak Chemical Communications (1979), 44(7), 2108-23

CODEN: CCCCAK; ISSN: 0366-547X

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



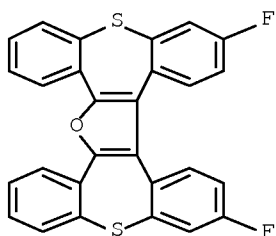
AB 4-Methoxy-2-(phenylthio)benzoic acid was transformed in 4 steps to the homologous acetic acid which was cyclized to 3-methoxydibenzo[b,f]-thiepin-10(11H)-one. Three further steps led to the 3-methoxy derivative of perathiepin (I, R = OMe) which was demethylated with BBr₃ to give I (R = OH). I (R = F) was prepared from (4-fluoro-2-iodophenyl)acetic acid, which was prepared by several procedures. Whereas I (R = OMe) had only mild tranquilizing activity, I (R = OH) was more potent than perathiepin in the tests for central depressant and cataleptic effects. I (R = F), while lacking the properties of a neuroleptic agent, was highly central depressant and this effect was prolonged after oral administration.

IT 73129-02-9F

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 73129-02-9 HCAPLUS

CN Bisdibenzo[2,3:6,7]thiepinino[4,5-b:4',5'-d]furan, 12,17-difluoro- (9CI)
(CA INDEX NAME)



L15 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1980:128852 HCAPLUS Full-text

DOCUMENT NUMBER: 92:128852

ORIGINAL REFERENCE NO.: 92:21015a,21018a

TITLE: Neurotropic and psychotropic agents. CXXIX.
Fluorinated neuroleptics of the 10-piperazino-10,11-dihydrodibenzo[b,f]thiepin series; 6-fluoro derivatives of perathiepin, octoclotheperin, doclotheperin and some related compounds

AUTHOR(S): Cervena, Irena; Metysova, Jirina; Bartl, Vaclav;
Protiva, Miroslav

CORPORATE SOURCE: Res. Inst. Pharm. Biochem., Prague, 130 00/3, Czech.
SOURCE: Collection of Czechoslovak Chemical Communications (1979), 44(7), 2139-55

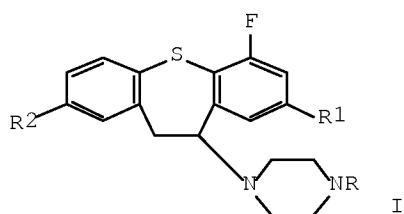
CODEN: CCCCAK; ISSN: 0366-547X

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 92:128852

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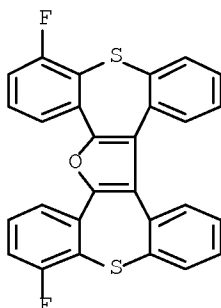


AB 6-Fluoro-10-piperazino-10,11-dihydrodibenzo[b,f]thiepins I (R = Me, CH₂CH₂OH, R₁ = H, R₂ = H, Cl; R = Me, R₁ = Cl, R₂ = H) were prepared via 2-(2-fluorophenylthio)phenylacetic acids, 6-fluorodibenzo[b,f]thiepin-10(11H)-ones, the corresponding 10-hydroxy and 10-chloro compds. as intermediates. Fluorination in position 6 did not greatly influence the pharmacol. profile of the compds., indicating that hydroxylation in position 6 is only a minor metabolic pathway. I (R = Me, R₁ = Cl, R₂ = H) is a potent central depressant and neuroleptic agent with some protraction of the sedative effects. Many of the compds. also had bactericidal, fungicidal, and tuberculostatic activity.

IT 73129-48-3F
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)

RN 73129-48-3 HCAPLUS

CN Bisdibenzo[2,3:6,7]thiepin[4,5-b:4',5'-d]furan, 1,9-difluoro- (9CI) (CA INDEX NAME)



L15 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1977:439416 HCAPLUS Full-text

DOCUMENT NUMBER: 87:39416

ORIGINAL REFERENCE NO.: 87:6219a,6222a

TITLE: Neurotropic and psychotropic agents. CV. Potential metabolites of noncataleptic neuroleptics: 2-chloro-8-hydroxy-10-(4-methylpiperazino)- and -10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[b,f]thiepin

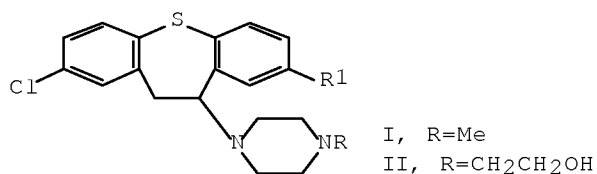
AUTHOR(S): Valenta, V.; Bartl, V.; Dlabac, A.; Metysova, J.; Protiva, M.

CORPORATE SOURCE: Res. Inst. Pharm. Biochem., Prague, Czech.

SOURCE: Collection of Czechoslovak Chemical Communications (1976), 41(12), 3607-27

CODEN: CCCCAK; ISSN: 0366-547X

DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



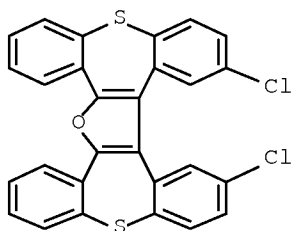
AB Starting from 5-chloro-2-(4-methoxyphenylthio)benzoic acid, 5 synthetic steps led to 2-chloro-8-methoxydibenzo(b,f)thiepin-10(11H)-one which was converted via 2 intermediates to 2-chloro-8-methoxy-10-(4-methylpiperazino)- and -10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo(b,f)thiepin (I and II, R1 = OMe). Demethylation with BBr₃ led to the title compds. I and II (R1 = OH), which are potential metabolites of noncataleptic neuroleptics doclothebin and VUFB-10032 (I and II, R1 = H). I and II (R1 = OH and OMe) have central depressant and cataleptic effects, the methoxy derivs. being more active than the hydroxy derivs. (LD₅₀ and ED₅₀ given). Modified methods of preparing 5-chloro-2-(phenylthio)benzoic acid and the corresponding alc. were described.

IT 63186-55-0P 63186-56-1P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)

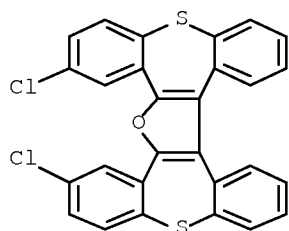
RN 63186-55-0 HCAPLUS

CN Bisdibenzo[2,3:6,7]thiepin[4,5-b:4',5'-d]furan, 13,16-dichloro- (9CI)
 (CA INDEX NAME)



RN 63186-56-1 HCAPLUS

CN Bisdibenzo[2,3:6,7]thiepin[4,5-b:4',5'-d]furan, 3,7-dichloro- (9CI) (CA INDEX NAME)



L15 ANSWER 7 OF 7 USPATFULL on STN

ACCESSION NUMBER: 2007:198145 USPATFULL Full-textTITLE: 1-Oxadibenzo[e,h]azulenes for the treatment of
central nervous system
diseases and disordersINVENTOR(S): Mercep, Mladen, Zagreb, CROATIA
Mesic, Milan, Zagreb, CROATIA
Pesic, Dijana, Sibenik, CROATIAPATENT ASSIGNEE(S): Pliva-Istrazivacki Institut d.o.o., Zagreb, CROATIA,
10000 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070173493	A1	20070726
APPLICATION INFO.:	US 2004-595935	A1	20041119 (10)
	WO 2004-HR52		20041119
			20060809 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	HR 2003-20030955	20031121 <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	DARBY & DARBY P.C., P.O. BOX 770, Church Street Station, New York, NY, 10008-0770, US	
NUMBER OF CLAIMS:	15	
EXEMPLARY CLAIM:	1	
LINE COUNT:	941	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the use of compounds from the group of 1-oxadibenzo[e,h]azulenes and of their pharmacologically acceptable salts and solvates in pharmaceutical formulation for the treatment and prevention of diseases, damages and disorders of the central nervous system (CNS) caused by disorders of the neurochemical equilibrium of biogenic amines or other neurotransmitters.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 199012-94-7D, Dibenzo[b,f]furo[2,3-d]oxepin, derivs.

628262-96-4 628262-97-5 628262-98-6

628262-99-7 628263-00-3 628263-01-4

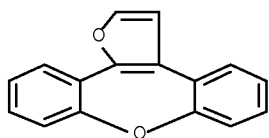
628263-02-5 628263-03-6 628263-04-7,

Dibenzo[b,f]furo[2,3-d]oxepin-2-methanol 628263-05-8

(oxadibenzoazulenes for treatment and prevention of CNS disorders by
modulating biogenic amines or other neurotransmitters)

RN 199012-94-7 USPATFULL

CN Dibenzo[b,f]furo[2,3-d]oxepin (9CI) (CA INDEX NAME)

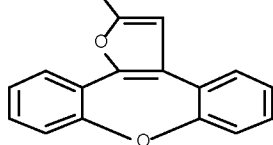


10/595,935

RN 628262-96-4 USPATFULL

CN 1-Propanamine, 3-(dibenzo[b,f]furo[2,3-d]oxepin-2-ylmethoxy)-N,N-dimethyl-
(CA INDEX NAME)

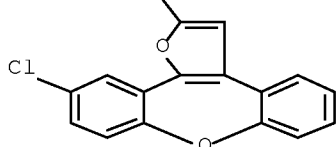
Me₂N—(CH₂)₃—O—CH₂



RN 628262-97-5 USPATFULL

CN Ethanamine, 2-[(11-chlorodibenzo[b,f]furo[2,3-d]oxepin-2-yl)methoxy]-N,N-
dimethyl- (CA INDEX NAME)

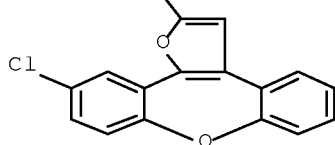
Me₂N—CH₂—CH₂—O—CH₂



RN 628262-98-6 USPATFULL

CN 1-Propanamine, 3-[(11-chlorodibenzo[b,f]furo[2,3-d]oxepin-2-yl)methoxy]-
N,N-dimethyl- (CA INDEX NAME)

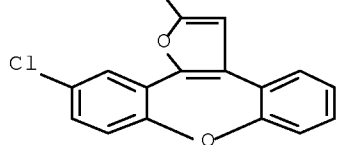
Me₂N—(CH₂)₃—O—CH₂



RN 628262-99-7 USPATFULL

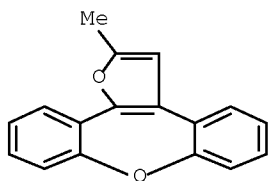
CN 1-Propanamine, 3-[(11-chlorodibenzo[b,f]furo[2,3-d]oxepin-2-yl)methoxy]-
(CA INDEX NAME)

H₂N—(CH₂)₃—O—CH₂



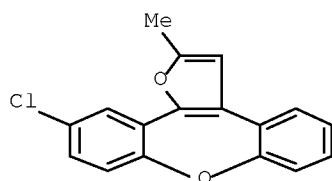
RN 628263-00-3 USPATFULL

CN Dibenzo[b,f]furo[3,2-d]oxepin, 2-methyl- (CA INDEX NAME)



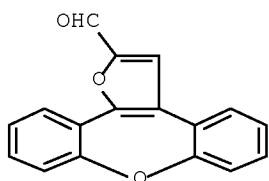
RN 628263-01-4 USPATFULL

CN Dibenzo[b,f]furo[2,3-d]oxepin, 11-chloro-2-methyl- (CA INDEX NAME)



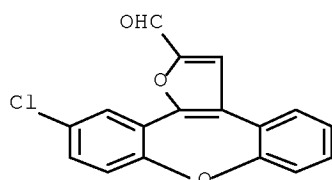
RN 628263-02-5 USPATFULL

CN Dibenzo[b,f]furo[3,2-d]oxepin-2-carboxaldehyde (CA INDEX NAME)



RN 628263-03-6 USPATFULL

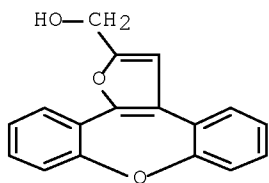
CN Dibenzo[b,f]furo[3,2-d]oxepin-2-carboxaldehyde, 11-chloro- (CA INDEX NAME)



RN 628263-04-7 USPATFULL

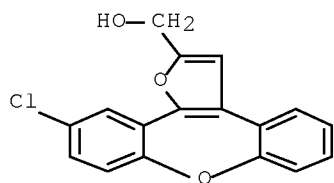
CN Dibenzo[b,f]furo[3,2-d]oxepin-2-methanol (CA INDEX NAME)

10/595,935



RN 628263-05-8 USPTFLL

CN Dibenzo[b,f]furo[3,2-d]oxepin-2-methanol, 11-chloro- (CA INDEX NAME)



SEARCH HISTORY

=> d his ful

(FILE 'HOME' ENTERED AT 13:14:24 ON 09 JUN 2008)

FILE 'HCAPLUS' ENTERED AT 13:14:35 ON 09 JUN 2008

E MERCEP MLADEN/AU

L1 54 SEA ABB=ON ("MERCEP MLADEN"/AU OR "MERCEP MLANDEN"/AU)
E MESIC MILAN/AU

L2 72 SEA ABB=ON ("MESIC M"/AU OR "MESIC MILAN"/AU)
E PESIC DIJANA/AU

L3 71 SEA ABB=ON ("PESIC D S"/AU OR "PESIC DEJAN"/AU OR "PESIC
DIJANA"/AU)

L4 25 SEA ABB=ON L1 AND L2 AND L3

L5 2 SEA ABB=ON L4 AND 1(W)?OXADIBENZO?
SELECT RN L5 1-2

FILE 'REGISTRY' ENTERED AT 13:15:42 ON 09 JUN 2008

L6 53 SEA ABB=ON (50-67-9/BI OR 51-41-2/BI OR 51-61-6/BI OR
56-86-0/BI OR 199012-94-7/BI OR 612837-28-2/BI OR 612837-29-3/B
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-9/BI OR 612837-60-2/BI OR 612837-61-3/BI OR 612837-62-4/BI OR
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-8/BI OR 612837-67-9/BI OR 628262-96-4/BI OR 628262-97-5/BI OR
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-4/BI OR 628263-02-5/BI OR 628263-03-6/BI OR 628263-04-7/BI OR
628263-05-8/BI)

FILE 'HCAPLUS' ENTERED AT 13:15:49 ON 09 JUN 2008

L7 2 SEA ABB=ON L5 AND L6

FILE 'REGISTRY' ENTERED AT 13:17:17 ON 09 JUN 2008

L8 STRUCTURE 628263-05-8

L9 1 SEA SSS SAM L8

L10 25 SEA SSS FUL L8

FILE 'HCAPLUS' ENTERED AT 13:19:13 ON 09 JUN 2008

L11 12 SEA ABB=ON L10

L12 6 SEA ABB=ON L11 AND (?CENTRAL?(W)?NERV?(W)?SYST? OR CNS OR
?NEUROCHEM?(W)?EQUIL? OR ?BIOGEN?(W)AMINE? OR ?NEUROTRANSMIT?)

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L13 1 SEA ABB=ON L11 AND (?CENTRAL?(W)?NERV?(W)?SYST? OR CNS OR
?NEUROCHEM?(W)?EQUIL? OR ?BIOGEN?(W)AMINE? OR ?NEUROTRANSMIT?)

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L14 7 DUP REMOV L12 L13 (0 DUPLICATES REMOVED)

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